Correction for urine glucose excretion

Matsuda Index

Use of a SGLT-2 inhibitor

$$\mathrm{HOMA-IR} = \frac{R_a}{(R_{au} - u)} \cdot \mathrm{HOMA-IR}_u$$

$$\text{Matsuda index} = \sqrt{\frac{(R_{au} - u)}{R_a} \cdot \frac{(D - u_D)}{D}} \cdot \text{Matsuda index}_u$$

where,

- HOMA-IR: true HOMA-IR, HOMA-IRu: apparent HOMA-IR with urine excretion
- Matsuda index: true Matsuda index, Matsuda indexD: apparent Matsuda index with urine exretion
- Ra: rate of appearance of glucose without urine excretion
- Rau: rate of appearance of glucose with urine exretion
- U: urine glucose exretion during basal state
- D: glucose load (=75g/analyzed time [min])
- u_D: urine glucose exretion during oral glucose load (excreted during analyzded time [g/min])

Correction for urine glucose excretion

Matsuda Index

Use of a SGLT-2 inhibitor

During basal steady state, R_d (glucose disposal) = R_a = ～ (R_{au} − u),
(R_{au} may be increased by the elevated level of glucagon
J Clin Invest. 2014 Feb 3;124(2):509-14.)

$$\mathrm{HOMA-IR} = \frac{R_a}{(R_{au} - u)} \cdot \mathrm{HOMA-IR}_u \cong \mathrm{HOMA-IR}_u$$

$$\text{Matsuda index} = \sqrt{\frac{(R_{au} - u)}{R_a} \cdot \frac{(D - u_D)}{D}} \cdot \text{Matsuda index}_u$$

$$\cong \sqrt{\frac{(D - u_D)}{D}} \cdot \text{Matsuda index}_u = \sqrt{\frac{(75 - u_D)}{75}} \cdot \text{Matsuda index}_u$$

where,

- HOMA-IR: true HOMA-IR, HOMA-IRu: apparent HOMA-IR with urine excretion
- Matsuda index: true Matsuda index, Matsuda indexD: apparent Matsuda index with urine exretion
- Ra: rate of appearance of glucose without urine excretion
- Rau: rate of appearance of glucose with urine exretion
- U: urine glucose exretion during basal state
- D: glucose load (=75g/analyzed time [min])
- u_D: urine glucose exretion during oral glucose load (excreted during analyzded time [g/min])

Correction for glucose dosage

Matsuda Index

$$\text{Matsuda index} = \sqrt{\frac{D_X}{D}} \cdot \text{Matsuda index}_X$$
$$= \sqrt{\frac{D_X}{75}} \cdot \text{Matsuda index}_X$$

where,
- Matsuda index: true Matsuda index,
- Matsuda index_x: apparent Matsuda index with urine exretion
- Dx: actual glucose dose applied
- D: glucose load for Matsuda index (=75g)

Start from HOMA

Induction of HOMA-IR (1)

$$\begin{cases} \dfrac{dg}{dt} = -k \cdot g + \dfrac{R_a}{V} \\ \dfrac{dk}{dt} = -a_1 \cdot k + a_2 \cdot i \end{cases}$$

Insulin sensitivity

$$S_I = \frac{a_2}{a_1}$$

a_1, a_2	**positive constant**
g, i	**plasma glucose, insulin conc.**
k	**the fractional disappearance rate of glucose (insulin action)**
V	**the volume of distribution of glucose**
R_a	**the glucose input rate**

(Radziuk J: *J Clin Endocrinol Metab* 85: 4426-4433, 2000)

Induction of HOMA-IR (2)

$$\begin{cases} \dfrac{dg}{dt} = -k \cdot g + \dfrac{R_a}{V} \\ \dfrac{dk}{dt} = -a_1 \cdot k + a_2 \cdot i \end{cases}$$

Steady state: $\begin{cases} \dfrac{dg}{dt} = 0 \\ \dfrac{dk}{dt} = 0 \end{cases}$

Insulin sensitivity （steady state）

$$S_I = \frac{k}{i} = \frac{a_2}{a_1} = \frac{R_a}{V \cdot g \cdot i} = \frac{R_a \div V}{g \cdot i}$$

$$\text{HOMA-IR}_0 = \frac{1}{S_I} = \frac{g \cdot i}{const}$$

(Radziuk J: *J Clin Endocrinol Metab* 85: 4426-4433, 2000)

Induction of HOMA-IR$_u$ with SGLT2I (1)

$$\begin{cases} \dfrac{dg}{dt} = -k \cdot g + \dfrac{R_a}{V} - \dfrac{u}{V} \\ \dfrac{dk}{dt} = -a_1 \cdot k + a_2 \cdot i \end{cases}$$

Insulin sensitivity

$$S_I = \frac{a_2}{a_1}$$

a_1, a_2	**positive constant**
g, i	**plasma glucose, insulin conc.**
k	**the fractional disappearance rate of glucose (insulin action)**
V	**the volume of distribution of glucose**
u	**the glucose excretion rate from urine**
R_a	**the glucose input rate**

(modified to Radziuk J: *J Clin Endocrinol Metab* 85: 4426-4433, 2000)

Induction of HOMA-IR$_u$ with SGLT2I (2)

$$\begin{cases} \dfrac{dg}{dt} = -k \cdot g + \dfrac{(R_a - u)}{V} \\ \dfrac{dk}{dt} = -a_1 \cdot k + a_2 \cdot i \end{cases}$$

Steady state: $\begin{cases} \dfrac{dg}{dt} = 0 \\ \dfrac{dk}{dt} = 0 \end{cases}$

Insulin sensitivity （steady state）

$$S_I = \frac{k}{i} = \frac{a_2}{a_1} = \frac{(R_a - u)}{V \cdot g \cdot i} = \frac{(R_a - u) \div V}{g \cdot i}$$

$$\text{HOMA-IR} = \frac{1}{S_I} = \frac{g \cdot i}{const'}$$

g, *i*, and S_I are different from those when u=0.

(modified to Radziuk J: *J Clin Endocrinol Metab* 85: 4426-4433, 2000)

HOMA-IR

$$\mathrm{HOMA\text{-}IR_u} = \frac{g_{0u} \cdot i_{0u}}{const}$$

HOMA-IR$_u$ is calculated by using the same way as HOMA-IR.

If insulin sensitivity (steady state) is the same,

$$\mathrm{HOMA\text{-}IR} = \frac{1}{S_I} = \frac{1}{S_{Iu}}$$

$$= \frac{g_{0u} \cdot i_{0u}}{(R_{au} - u) \div V} = \frac{g_{0u} \cdot i_{0u}}{R_a \div V} \cdot \frac{R_a \div V}{(R_{au} - u) \div V}$$

$$= \mathrm{HOMA\text{-}IR_u} \cdot \frac{R_a}{(R_{au} - u)}$$

$$g_0 \cdot i_0 = (g_{0u} \cdot i_{0u}) \cdot \frac{R_a}{(R_{au} - u)}$$

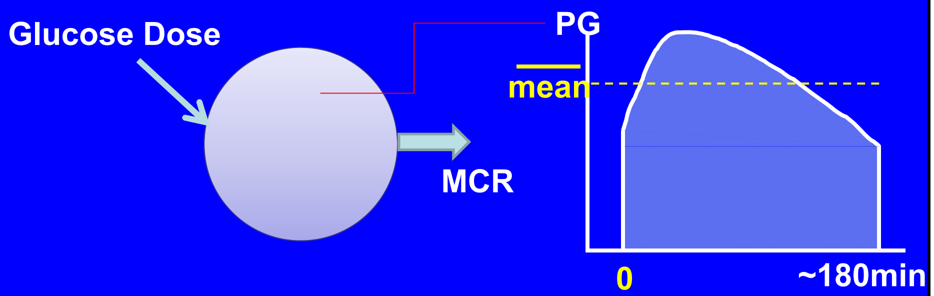
Oral glucose administration

After glucose administration

MCR (metabolic clearance rate)

$$= \frac{\text{Dose of glucose}}{\text{AUC of PG conc.}}$$

(non- steady state)



After glucose administration

Insulin Sensitivity during OGTT

can be estimated by

$$\frac{\text{MCR of glucose}}{\text{Average Insulin conc.}}$$

$$= \frac{\text{Dose of glucose}}{\overline{\text{PG}} \times \overline{\text{Insulin}}}$$

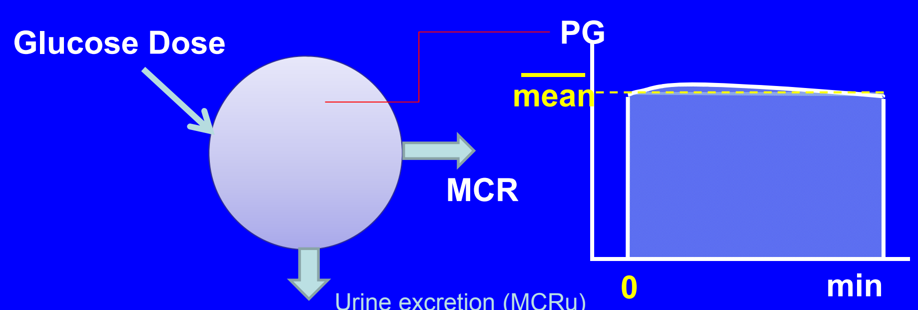
Oral glucose administration

Basal with a SGLT-2 inhibitor

In response to glucose appearance
(BASAL STATE)

$$\text{MCR} + \text{MCRu} = \frac{\text{Endogenous Glucose Production[mg/min]}}{\text{AUC of PG conc.}}$$

$$\text{MCRu} = \frac{\text{Urine Glucose Excretion [mg/min]}}{\text{AUC of PG conc.}}$$



In response to glucose appearance
(BASAL STATE)

Insulin Sensitivity during Basal State

can be estimated by

$$\frac{\text{MCR of glucose}_0}{\text{Average Insulin conc.}_0}$$

When UGE = 0,

$$= \frac{EGP_0}{\overline{PG_0} \times \overline{Insulin_0}} = \frac{EGP_0}{k \times \text{HOMA-IR}}$$

HOMA-IR = $\overline{PG}_0$ x $\overline{Insulin}_0$ / k

k: constant

In response to glucose administration
(BASAL STATE)

$$MCR_u = \frac{\text{Endogenous Glucose Production}_u\ [\text{mg/min}]}{\text{AUC of PG conc.}_u} - \frac{\text{Urine Glucose Excretion [mg/min]}}{\text{AUC of PG conc.}_u}$$

EGP: Endogenous Glucose Production

UGE: Urine Glucose Excretion

In response to glucose appearance
(BASAL STATE)

Insulin Sensitivity during Basal State

can be estimated by

$$\frac{MCR_u}{\text{Average Insulin conc.}_u} = \frac{EGP_u - UGE}{\overline{PG_u} \times \overline{Insulin_u}} = \frac{EGP_u - UGE}{k \times \text{HOMA-IR}_u}$$

$\text{HOMA-IR}_u = PG_u \times Insulin_u / k$

k: constant

If insulin sensitivity is the same despite of urine glucose excretion,

$$\frac{MCR_u}{\overline{Insulin_u}} = \frac{MCR_0}{\overline{Insulin_0}}$$

$$\frac{EGP_u - UGE}{k \times \text{HOMA-IR}_u} = \frac{EGP_0}{k \times \text{HOMA-IR}_0}$$

$$\text{HOMA-IR}_0 = \frac{EGP_0}{EGP_u - UGE} \cdot \text{HOMA-IR}_u$$

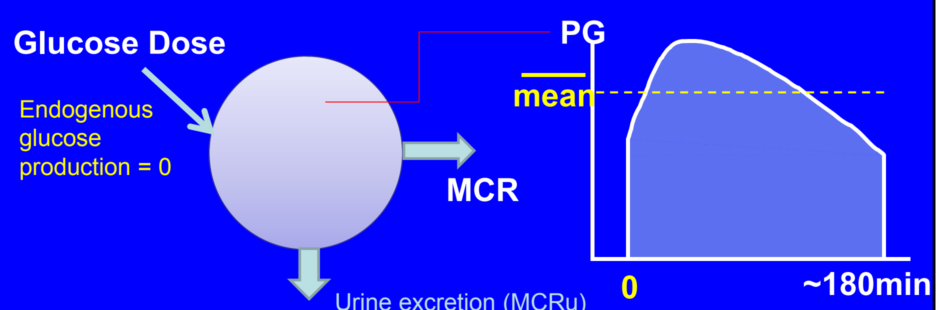
Oral glucose administration

Glucose loading with a SGLT-2 inhibitor

After glucose administration （OGTT）

$$\mathrm{MCR} + \mathrm{MCRu} = \frac{\text{Dose of glucose}}{\text{AUC of PG conc.}}$$

(non- steady state)



After glucose administration （OGTT）

$$MCR_u = \frac{\text{Dose of glucose [mg/min]}}{\text{AUC of PG conc.}_u} - \frac{\text{Urine Glucose Excretion [mg/min]}}{\text{AUC of PG conc.}_u}$$

D: Dose of glucose
UGE: Urine Glucose Excretion

After glucose administration （OGTT）

Insulin Sensitivity
can be estimated by

$$\frac{MCR_u}{\text{Average Insulin conc.}_u} = \frac{D - UGE}{\overline{PG_u} \times \overline{Insulin_u}}$$

If insulin sensitivity is the same despite of urine glucose excretion,

$$\frac{MCR_u}{\overline{Insulin_u}} = \frac{MCR_0}{\overline{Insulin_0}}$$

$$\frac{D - UGE}{\overline{PG_u} \times \overline{Insulin_u}} = \frac{D}{\overline{PG_0} \times \overline{Insulin_0}}$$

Correction to Matsuda index

Glucose loading with a SGLT-2 inhibitor

When a SGLT-2 inhibitor is used,

$$\text{Matsuda index}_u = \frac{10000}{\sqrt{g_{0u} \cdot i_{0u} \cdot g_u \cdot i_u}}$$

$$g_0 \cdot i_0 = (g_{0u} \cdot i_{0u}) \cdot \frac{R_a}{(R_{au} - u)} \qquad g \cdot i = (g_u \cdot i_u) \cdot \frac{D}{(D - u_D)}$$

$$\text{Matsuda index} = \frac{10000}{\sqrt{g_0 \cdot i_0 \cdot g \cdot i}}$$

$$= \frac{10000}{\sqrt{(g_{0u} \cdot i_{0u}) \cdot \frac{R_a}{(R_{au} - u)} \cdot (g_u \cdot i_u) \cdot \frac{D}{(D - u_D)}}}$$

When a SGLT-2 inhibitor is used,

$$\text{Matsuda index}$$

$$= \frac{\text{Matsuda index}_u}{\sqrt{\frac{R_a}{(R_{au} - u)} \cdot \frac{D}{(D - u_D)}}}$$

$$= \sqrt{\frac{(R_{au} - u)}{R_a} \cdot \frac{(D - u_D)}{D}} \cdot \text{Matsuda index}_u$$